REMARKS

1. **Status of the claims**

New claims 32 and 33 define the virally safe aqueous albumin solution with the expression "in which the transport and binding sites of therapeutically active ingredients are available in the albumin."

Support for new claims 32 and 33 can be found at page 1, lines 22-24 of the application as filed.

No new matter has been added.

2. **Claim rejection under 35 U.S.C. §112**

Claims 30-31 are rejected under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

The process of the present invention leads to a virally safe aqueous albumin solution as described in [0015] of the application. Applicant has found that, in the context of the invention, using a judicious combination of pH, ionic strength, albumin concentration and temperature (and consequently viscosity) values, in the aqueous albumin solution submitted to the nanofiltration step, makes it possible to reach an efficient optimization of the albumin recovery yield, and rates of reduction of viruses and other undesirable macromolecules higher than the limits set by the control authorities (4 log).

Moreover, in the context of the invention, the virally safe aqueous albumin solution submitted to the nanofiltration is characterised in that the transport and binding sites of therapeutically active ingredients are available in the albumin. The albumin according to the invention retains its binding and transport potential of various active ingredients, and through this binding, reduces their toxicity or increases the bioavailability by a depot effect.

The properties of albumin nanofiltered without any stabiliser, in the transport and binding of medicines, are studied by comparing them with those obtained with two different albumin A batches pasteurised in the presence of sodium caprylate as shown in example 12, pages 26-29.

Withdrawal of the corresponding rejection is thus respectfully requested.

Claims 30-31 are rejected under 35 U.S.C. § 112 as being indefinite for failing to identify the ionic strength by units of either molarity or molality.

Applicant submits that it should be made clear that, in the context of the invention, the ionic strength is defined by molality.

For example, at page 19 of the present application it is disclosed that albumin solutions are prepared in purified water in a NaCl solution at 9 g/L with an ionic strength of 0.15. One skilled in the art would have understood from this Example 7, that the **molality**[1] of a solution m_i is defined as the amount of a constituent n_i divided by the mass of the solvent $m_{solvent}$ (NaCl = 58 g/mol) and in the present case the molality corresponds to 9/58= 0.15 mol/L.

Withdrawal of the corresponding rejection is thus respectfully requested.

3. Claim rejection under 35 USC §103

Claims 30-31 are rejected as being unpatentable over Ohmura (EP 0 570 916), in view of Lengsfeld et al. (U.S. 2003/0232969) and Winge (U.S. 6,399,357 B1).

Applicant respectfully disagrees for the following reasons:

a) EP 0 570 916 teaches a process for producing a recombinant human serum albumin comprising the steps 1-8) (see EP 0 570 916, from page 2, line 50 to page 3, line 11).

EP 0 570 916 does not disclose a nanofiltration step.

Further, it unambiguously appears in EP 0 570 916, that the resulting albumin solution is conditioned for pharmaceutical use, through the addition of acetyltryptophan or a salt thereof, and sodium caprylate:

> *"another object of the instant invention is to provide a pharmaceutical preparation comprising recombinant human serum albumin, acetyltryptophan or a salt thereof and sodium caprylate."* (see EP 0 570 916, page 3, lines 15-16 and claim 11)

> *"The resulting pharmaceutical preparation consisted of 25% HAS, 0.02M acetyltryptophan sodium salt and 0.0M sodium caprylate."* (see EP 0 570 916, page 16, example 10, lines 39-40)

[1] http://en.wikipedia.org/wiki/Molality

Applicant submits that the binding properties of the albumin obtained by the process of the present invention appear to be significantly higher than those of an albumin which was prepared with a process comprising a heat-treatment step. This interpretation is fully supported by the results disclosed in Example 12 of the present application. In this example, the properties in the transport and binding of medicines of an albumin nanofiltered without any stabilizer are studied by comparing them with those of two different albumin batches pasteurised in the presence of sodium caprylate. As disclosed in Tables 10 and 11 (pages 28 and 30), and summarized in Table 12 (page 31), the albumin resulting from the process of the invention (noted "A'4") displays binding constants (Ka) for diazepam and warfarine which are significantly higher than those of the heat-treated albumins.

To sum up, EP 0 570 916 fails to teach:

- a virally safe aqueous albumin solution obtained by nanofiltration
- a virally safe aqueous albumin solution in which the transport and binding sites of therapeutically active ingredients are available in the albumin.

b) Winge (U.S. 6,399,357 B1) teaches a method of virus-filtering a solution containing at least one molecule, and in particular albumin, wherein the total salt content of the solution is fixed in a range of from about 0.2M up to saturation.

Moreover it should be noted that Examples 3 and 22 of U.S. 6,399,357 are the only examples which relate to filtering of protein solutions actually containing viral particles that were actually added to the protein solutions, without any information concerning the concentration. In Examples 3 and 22, the salt concentrations of solutions comprising virus particles are 0.15M (as control) and 1.0M, the pH of the solution is 7.0, and protein concentration is 0.5-1.0 A_{280} (absent any reference for determining the actual value of a A_{280} unit). It is more particularly to be noted that neither Example 3 nor Example 22 actually concerns a solution comprising albumin.

It is thus submitted that the results and conclusions obtained from the other Examples (1-2 and 4-21), relating to filtering of solutions comprising macromolecules (and in particular albumin), devoid of virus particles and with a salt concentration of up to 1.5M, cannot be used to

extrapolate results concerning the efficiency of virus removal as if virus was present in these solutions.

It further appears that all examples of U.S. 6,399,357 relate to the filtration of relatively high purity protein solutions. However, there is nothing in the Specification to indicate what is meant by the term "pure" protein solutions. Example 12 of U.S. 6,399,357 in particular explicitly discloses that the solution of albumin subjected to the filtration process was supplied by Pharmacia AB, Stockholm, Sweden (see column 12, lines 19-22), and was thus prepared through classical purification procedures possibly comprising a pasteurisation step in presence of stabilizers such as sodium caprylate.

U.S. 6,399357 therefore contains no indication in the Specification of how the removal of virus will be affected by carrying out a filtration method (which refers to any filtering process without limitation) using solutions with total salt of "up to saturation," varying any number of filtration parameters (*e.g.* macromolecule concentration of the solution, pH of the solution, purity of the material to be filtered, the flow rate through the membrane, the type of filter, etc.). It is indeed in the common knowledge of the skilled person in the art that the performances of the filtration methods, in particular the effectiveness of nanofiltration towards the anti-viral filtration and the resulting protein concentration is influenced by various parameters, like the nature of the filtration membrane, pH, ionic strength, etc.

To sum up, U.S. 6,399,357 fails to teach:

- a virally safe aqueous albumin solution obtained by nanofiltration
- a virally safe aqueous albumin solution in which the transport and binding sites of therapeutically active ingredients are available in the albumin.

Finally, Applicant considers that the teachings of U.S. 6,399,357 do not rescue the deficiencies of EP 0 570 916.

Accordingly, the rejection over EP 0 570 916 in view of U.S. 6,399,357 fails to make a *prima facie* case of obviousness, and the rejection should be withdrawn

The Examiner asserts that "*one of ordinary skill in the art would have been motivated to look for a supplementary step which could assure the intended product to achieve the required purity. Filtration is routine operation to improve the purity of a protein. Further, one ordinary*

skill in the art would be motivated to employ nanofiltration, because Winge discloses the purification albumin using a nanofilter (see particularly claim 14-17 and 35-42)"

However, contrary to the Examiner's assertion, U.S. 6,399,357 does not teach or suggest the nanofiltration of albumin using specific and well defined filtration parameters. Indeed, nowhere in U.S. 6,399,357 is there any description of a process for producing a virally safe aqueous albumin solution, in which the transport and binding sites of therapeutically active ingredients are available in the albumin.

Furthermore, it appears that the Examiner is using impermissible hindsight to reconstruct the present invention by picking and choosing elements from different references when there is no motivation to combine any one or more of their respective disclosures into a single claimed embodiment. *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1988) ("Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention."); *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991) ("We do not 'pick and choose among the individual elements of assorted prior art references to recreate the claimed invention,' but rather, we look for 'some teaching or suggestion in the references to support their use in the particular claimed combination.").

Even if it would have been obvious to the skilled artisan to use known purification techniques such as nanofiltration for removal of virus, nanofiltration would have been considered for use as step additional to chromatography on chelate resin (step 8) according to only a very narrow range of filtration conditions as disclosed in U.S. 6,399,357. These conditions comprise a pH range of 5.5 to 7.4, a protein concentration between 0.5-10.0 A_{280} units (absent any reference for the actual value of an A_{280} unit), and a salt concentration not exceeding 1.5M.

The inventor of U.S. 6,399,357 found that virus filtration can be effected much more effectively than previously known, by increasing the salt content of the solution. This discovery was considered surprising, because previously in virus filtration of proteins it was believed that solely the protein concentration, the rate of flow and the pH had any influence on the process (column 2, l35-42).

On the contrary, surprisingly, the Applicant of the present invention has found that decreasing ionic strength is correlated with a better viral reduction (page 7, 123-25) in relation to the nanofiltration of an aqueous albumin solution.

It is therefore submitted that the results and conclusions disclosed in U.S. 6,399,357 relating to filtering various proteins cannot be generalized and applied directly to the albumin nanofiltration.

The present invention allows the preparation of a virally safe aqueous albumin solution in which the transport and binding sites of therapeutically active ingredients are available in the albumin by controlling the process parameters of the entire system (albumin, temperature, flow rates, pH, ionic strength).

Even if one were to find motivation within the U.S. 6,399,357 reference to "optimize" the parameters that may influence viral clearance and albumin passage, it would have been unclear what properties were to be optimized or for what purpose. U.S. 6,399,357 uses a set of distinct physicochemical parameters.

c) Lengsfeld et al. (U.S. 2003/0232969) relates to the nanofiltration of protein solutions, by means of which it is possible to separate off viruses virtually completely. This object can be achieved by a method comprising adding to a protein solution at least one chaotropic substance.

The specification of Lengsfeld does not add anything to the defects of its claims which would suggest the present invention since Lengsfeld is silent about some parameters of the process (pH, ionic strength, albumin concentration and temperature) which are known to have a direct impact on the viral clearance of product.

In view of these elements, Applicant therefore considers that the skilled person in the art, would have had no reasonable expectation of success to prepare the albumin solution with rates of reduction of viruses and other undesirable macromolecules higher than the limits set by the control authorities (4 log), in view of the teachings of EP 0 570 916 in view of U.S. 6,399,357 and U.S. 2003/0232969.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicant submits that the claims are now in condition for allowance, and respectfully request formal notification to that effect.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant respectfully petitions for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $490.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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